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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,973	CERTA ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *15-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/04,6/04, 11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-43 are pending.

Applicant's election of Group I, Claim 1-14 and 43 and subgroup (A) protein of PDE4D3 in the reply filed on 7/10/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in communication filed on 7/10/2006.

Claims 1-14 and 43 are under consideration and are being examined herein.

Priority

Acknowledgement is made of applicants claim for foreign priority of EP 02028057.4 filed on 12/17/2002.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 11/22/2004, 6/18/2004, and 3/17/2004 /2003 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

Thcre is no drawing with this application.

Claim Objections

Claims 1-4, and 7-9 are objected to with the recitation "PDE", as abbreviations should not be used without at least once fully setting forth what they are used for. Appropriate correction is required.

Claims 3 and 4 are objected to with the recitation "PDE4", as abbreviations should not be used without at least once fully setting forth what they are used for. Appropriate correction is required.

Claims 7 and 8 are objected to with the recitation "LF1", as abbreviations should not be used without at least once fully setting forth what they are used for. Appropriate correction is required.

Claims 7 and 9 are objected to with the recitation "UCR1", as abbreviations should not be used without at least once fully setting forth what they are used for. Appropriate correction is required.

Claim 10 is objected to as encompassing non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-14 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite and vague in the recitation of the "decreased aggregate formation" which is confusing. The phrase "decreased" compared to what? Accordingly, claims 2-14 and 43 are rejected, as they are dependent on claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3, 4 and 10 are directed to a genus of any modified phosphodiesterase (PDE) or any modified PDE4 or any isoform of PDE4D or any PDE4D3 from any source having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE4D3. Claim 1 also recites that said PDE polypeptide exhibiting decreased aggregate formation and claim 2 recites the polypeptide, wherein said PDE polypeptide sequence is a long form PDE polypeptide sequence. Claim 3 recites the polypeptide, wherein said PDE polypeptide sequence is a PDE4 polypeptide sequence and claim 4 recites the polypeptide sequence is a PDE4D polypeptide sequence. Claim 5 recites the PDE4D polypeptide, wherein the proportion of non-aggregated

polypeptide in the total polypeptide is from 55% to 100% of total polypeptide and claim 6 recites the PDE polypeptide, wherein the proportion of non-aggregated polypeptide in the total polypeptide is from 55% to 100% of total polypeptide. Claim 7 recites the PDE polypeptide, wherein the polypeptide sequence starts at any amino acid located between the LF 1 splice site and the first amino acid of the UCR1 start of the native PDE polypeptide and claim 8 recites the PDE polypeptide, wherein the polypeptide sequence starts at the LF1 splice site of the native PDE polypeptide. Claim 9 recites the PDE polypeptide, wherein the PDE polypeptide sequence start is located 13 amino acids upstream of the UCR1 start of the native PDE polypeptide and claim 10 recites the PDE4D polypeptide, wherein the PDE4D polypeptide sequence is a D3. Claim 11 recites the PDE polypeptide, wherein said polypeptide comprises one or more mutations of Serine residues and claim 12 recites the PDE polypeptide, wherein said Serine residues are mutated to either Alanine or Aspartic acid. Claim 13 recites the PDE polypeptide, wherein said Serine residues are selected from the group consisting of Ser54 and Ser579 and claim 14 recites the PDE polypeptide, wherein said polypeptide exhibits decreased tubulin association. Claim 43 recites a crystallized PDE polypeptide. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately

described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification teaches the structure of only a single representative species of PDE4D3 protein and a few representative species of PDE4D proteins, and a few representative species of PDE proteins.

Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding PDE, PDE4 and PDE4D3 proteins having decreased aggregate formation. Given this lack of description of representative species encompassed by the genus of proteins of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-14 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified by N-terminal deletion splice variant PDE4D3 of SEQ ID NO: 1 from human, does not reasonably provide enablement for any modified phosphodiesterase (PDE) or any modified PDE4 or any isoform of PDE4D or any PDE4D3 from any source having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE4D3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 3-4 and 10 are so broad as to encompass any modified phosphodiesterase (PDE) or any modified PDE4 or any isoform of PDE4D or any PDE4D3 from any source having

an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE. Claim 1 also recites that said PDE polypeptide exhibiting decreased aggregate formation and claim 2 recites the polypeptide, wherein said PDE polypeptide sequence is a long form PDE polypeptide sequence. Claim 3 recites the polypeptide, wherein said PDE polypeptide sequence is a PDE4 polypeptide sequence and claim 4 recites the polypeptide sequence is a PDE4D polypeptide sequence. Claim 5 recites the PDE4D polypeptide, wherein the proportion of non-aggregated polypeptide in the total polypeptide is from 55% to 100% of total polypeptide and claim 6 recites the PDE polypeptide, wherein the proportion of non-aggregated polypeptide in the total polypeptide is from 55% to 100% of total polypeptide. Claim 7 recites the PDE polypeptide, wherein the polypeptide sequence starts at any amino acid located between the LF 1 splice site and the first amino acid of the UCRI start of the native PDE polypeptide and claim 8 recites the PDE polypeptide, wherein the polypeptide sequence starts at the LF1 splice site of the native PDE polypeptide. Claim 9 recites the PDE polypeptide, wherein the PDE polypeptide sequence start is located 13 amino acids upstream of the UCRI start of the native PDE polypeptide and claim 10 recites the PDE4D polypeptide, wherein the PDE4D polypeptide sequence is a D3. Claim 11 recites the PDE polypeptide, wherein said polypeptide comprises one or more mutations of Serine residues and claim 12 recites the PDE polypeptide, wherein said Serine residues are mutated to either Alanine or Aspartic acid. Claim 13 recites the PDE polypeptide, wherein said Serine residues are selected from the group consisting of Ser54 and Ser579 and claim 14 recites the PDE polypeptide, wherein said polypeptide exhibits decreased tubulin association. Claim 43 recites a crystallized PDE polypeptide. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large

number of PDE or splice variants PDE4D or mutants broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one PDE4D3, a few PDE4 and a few PDE.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims, which encompass any modified phosphodiesterase (PDE) or any modified PDE4 or any isoform of PDE4D or any PDE4D3 having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting PDE activity; (B) the general tolerance of PDE to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any PDE residues with an expectation of obtaining the desired biological function; and (D) the

specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any modified phosphodiesterase (PDE) or any modified PDE4 or any isoform of PDE4D or any PDE4D3 having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any PDE having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bolger et al. (Characterization of five different proteins produced by alternatively spliced mRNAs from the human cAMP-specific phosphodiesterase PDE4D gene, Biochem J. 1997 Dec 1; 328 (Pt 2): 539-48). Bolger et al. teach human PDE polypeptides including N-terminal deleted (1-78 amino acid) (see page 543, column 2) PDE as well as alternatively spliced variant such as PDE4D3

polypeptide, which is 100% identical to the PDE4D3 sequence of instant application having cAMP-specific phosphodiesterase activity. Bolger et al. also teach that PDE4D3 is a membrane bound (very firmly) PDE, which is not soluble in aqueous buffer i.e. 95% insoluble or aggregated but 93% soluble in NaCl+Triton-X-100 solution. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE, having a splice site (LF1) and upstream conserved region (UCR1). Bolger et al. furthermore teach that several amino acid residues upstream of UCR1 is the start site of native PDE polypeptide. It is widely known in the art that PDE has a transmembrane region comprising 6 hydrophobic helices at the N-terminus (1-250 amino acid) of PDE and deletion of whole any one of the six helices have reduce aggregation. Since, Bolger et al. teach a N-terminal 1-78 amino acid deleted PDE, therefore, PDE of Bolger et al. inherently possesses reduced aggregating characteristics or more soluble properties. Therefore, Bolger et al. anticipates claims 1-4 and 10 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-7 are rejected under 35 U.S.C. 103 (a) as being obvious over Bolger et al. (Characterization of five different proteins produced by alternatively spliced mRNAs from the human cAMP-specific phosphodiesterase PDE4D gene, Biochem J. 1997 Dec 1; 328 (Pt 2): 539-48) in view of Shakur et al. (Engineered deletion of the unique N-terminal domain of the cyclic AMP-specific phosphodiesterase RD1 prevents plasma membrane association and the attainment of enhanced thermostability without altering its sensitivity to inhibition by rolipram. Biochem J. 1993 Jun 15; 292 (Pt 3): 677-86). Bolger et al. teach human PDE polypeptides including N-terminal 1-78 amino acid residues deleted (see page 543, column 2) PDE as well as alternatively spliced variant PDE4D3 polypeptide, which is 100% identical to the PDE4D3 sequence of instant application having cAMP-specific phosphodiesterase activity. Bolger et al. also teach that PDE is a membrane bound (very firmly) PDE, which is not soluble in aqueous buffer i.e. 95% insoluble or aggregated but 93% soluble in NaCl+Triton-X-100 solution. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE, having a splice site (LF1) and upstream conserved region (UCR1). Bolger et al. furthermore teach that the start site of native PDE polypeptide, which is several amino acid residues upstream of UCR1 region. Bolger et al. do not teach deleted Bolger et al. do not teach an N-terminally deleted PDE, which starts at any point between LF1 and UCR1 region (claim 7)

or starts at splice site (LF1) (claim 8) or start 13 amino acid upstream of UCR1 region on that the N-terminally deleted PDE would have reduced aggregate formation i.e. solubility would increase due to deletion mutation. Shakur et al. teach an engineered deletion of the unique N-terminal domain of the cyclic AMP-specific phosphodiesterase prevents plasma membrane association and the attainment of enhanced thermostability without altering the activity. Shakur et al. also teach that removal of the first 67 nucleotides of the PDE gene yielded a truncated enzyme, which lacked the N-terminal first 25 amino acids, wherein the PDE activity was found exclusively in the cytosol fraction not in membrane bound indicating that truncated PDE does not have membrane binding residues, which results in aggregate formation.

Shakur et al. clearly identified the membrane-binding region (N-terminal 1-25) of PDE by using deletion mutation of PDE protein and determined by measuring PDE enzyme activity in cytosol (soluble) fraction not in palette containing membrane fraction suggesting that N-terminal region involvement in aggregate or insolubility characteristics of PDE protein.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to delete the human PDE of Bolger et al. at the N-terminal region (between UCR1 and splice site) as taught by Shakur et al. to reduce the membrane-binding activity thereby reducing aggregate formation as taught by Shakur et al. to produce a PDE protein in soluble form.

One of ordinary skill in the art would have been motivated for deleting N-terminal region of PDE protein to convert insoluble protein to soluble protein, which is easy to handle for using this soluble protein for identifying inhibitors and activators of said PDE protein, which is important for commercial and therapeutic purpose.

Claims 11-13 are rejected under 35 U.S.C. 103 (a) as being obvious over Bolger et al. (Characterization of five different proteins produced by alternatively spliced mRNAs from the human cAMP-specific phosphodiesterase PDE4D gene, Biochem J. 1997 Dec 1; 328 (Pt 2): 539-48) in view of MacKenzie et al. (Long PDE4 cAMP specific phosphodiesterases are activated by protein kinase A-mediated phosphorylation of a single serine residue in Upstream Conserved Region 1 (UCR1), Br J Pharmacol. 2002 Jun; 136(3): 421-33). Bolger et al. teach human PDE polypeptides including N-terminal 1-78 amino acid residues deleted (see page 543, column 2) PDE as well as alternatively spliced variant PDE4D3 polypeptide, which is 100% identical to the PDE4D3 sequence of instant application having cAMP-specific phosphodiesterase activity. Bolger et al. also teach that PDE4D3 is a membrane bound (very firmly) PDE, which is not soluble in aqueous buffer i.e. 95% insoluble or aggregated. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE, having a splice site (LF1) and upstream conserved region (UCR1). Bolger et al. furthermore teach that the start site of native PDE polypeptide, which is several amino acid residues upstream of UCR1 region. Bolger et al. do not teach mutations at one or more serine residues of PDE protein. Mackenzie et al. teach a human PDE polypeptide, more specifically alternatively spliced variant PDE4D3 polypeptide having cAMP-specific phosphodiesterase activity. MacKenzie et al. also teach one or more mutation of serine residues of PDE4D3 polypeptide, wherein serine at position 54 (Ser54) is mutated to alanine residue. MacKenzie et al. also teach serine residue at position 579 in PDE4D3 polypeptide. Mackenzie et al. also suggest that inhibiting PKA-specific activation of PDE, which might improve cognitive function, asthma, depression, and stroke or cardiac reperfusion injury.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to combine the teachings of Bolger et al. and Mackenzie et al. to introduce a mutation at Ser54 on N-terminal deleted PDE protein of Bolger et al. by using the methods of mutating serine residues specially serine at position 54 (Ser54) to alanine residue as taught by Mackenzie et al. to make a PDE polypeptide non-phosphorylated at position 54 by PKA as determine by phospho-serine54 specific antibody, which leads to decrease PDE activity that may inhibit cellular desensitization processes in cells, thereby enhance cell to cell communication through cAMP signal transduction machinery, which might have beneficial role on improving cognitive function, asthma, depression, stroke or cardiac reperfusion injury.

Claim 14 is rejected under 35 U.S.C. 103 (a) as being obvious over Bolger et al. (Characterization of five different proteins produced by alternatively spliced mRNAs from the human cAMP-specific phosphodiesterase PDE4D gene, Biochem J. 1997 Dec 1; 328 (Pt 2): 539-48) see SOS in view of Bifulco et al. (2',3'-Cyclic nucleotide 3'-phosphodiesterase: a membrane-bound, microtubule-associated protein and membrane anchor for tubulin, Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):1807-12. Epub 2002 Feb 12). Bolger et al. teach human PDE polypeptides including N-terminal 1-78 amino acid residues deleted (see page 543, column 2) PDE as well as alternatively spliced variant PDE4D3 polypeptide, which is 100% identical to the PDE4D3 sequence of instant application having cAMP-specific phosphodiesterase activity. Bolger et al. also teach that PDE4D3 is a membrane bound (very firmly) PDE, which is not soluble in aqueous buffer i.e. 95% insoluble or aggregated. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE, having a splice site (LF1)

and upstream conserved region (UCR1). Bolger et al. furthermore teach that the start site of native PDE polypeptide is several amino acid residues upstream of UCR1 region. Bolger et al. do not teach the decreased association of PDE protein with tubulin.

However, Bifulco et al. teach a cAMP-specific phosphodiesterase, which is firmly associated with tubulin through C-terminal region of PDE and enhance microtubule assembly. Bifulco et al. further teach the association of PDE and tubulin could be reduced by phosphorylation of the phosphodiesterase protein by PKC or deletion of C-terminus of phosphodiesterase protein, which results in interference of phosphodiesterase and tubulin association. Bifulco et al. also teach the association between PDE and tubulin cause tubulin polymerization, which results in cancer for developing anticancer agent.

One of ordinary skilled in the art would have been motivated for reducing PDE and tubulin association because the association between PDE and tubulin cause tubulin polymerization, which results in cancer for developing anticancer agent for therapeutic purpose.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to check whether there is any interaction between the N-terminal deleted PDE polypeptide and tubulin or role of PDE on tubulin assembly formation or polymerization as taught by Bifulco et al. Bifulco et al. clearly show the interaction between PDE and tubulin through C-terminal region of PDE and deleting PDE at C-terminal region or phosphorylation of PDE protein results in the reduced PDE and tubulin association.

Claim 43 is rejected under 35 U.S.C. 103 (a) as being obvious over Bolger et al. (Characterization of five different proteins produced by alternatively spliced mRNAs from the

human cAMP-specific phosphodiesterase PDE4D gene, Biochem J. 1997 Dec 1; 328 (Pt 2): 539-48) in view of Lee et al. (Crystal structure of phosphodiesterase 4D and inhibitor complex (1), FEBS Lett. 2002 Oct 23; 530(1-3): 53-8). Bolger et al. teach human PDE polypeptides including N-terminal deleted (see page 543, column 2) PDE as well as alternatively spliced variant such as PDE4D3 polypeptide, which is 100% identical to the PDE4D3 sequence of instant application having cAMP-specific phosphodiesterase activity. Bolger et al. also teach that PDE4D3 is a membrane bound (very firmly) PDE, which is not soluble in aqueous buffer i.e. 95% insoluble or aggregated but 93% soluble in NaCl+Triton-X-100 solution. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE, having a splice site (LF1) and upstream conserved region (UCR1). Bolger et al. furthermore teach that several amino acid residues upstream of UCR1 is the start site of native PDE polypeptide. Bolger et al. do not teach the crystallized polypeptide of PDE. Lee et al. teach a crystal structure of cAMP-specific phosphodiesterase, specifically isoform PDE4D.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to produce a crystal structure of N-terminal deleted PDE protein of Bolger et al. by using the method of Lee et al. to produce a crystallized PDE polypeptide to understand the molecular structure of N-terminal deleted PDE for targeting that polypeptide by inhibitors for therapeutic intervention against specific diseases caused by active PDE proteins.

One of ordinary skill in the art would have a reasonable expectation of success in crystallizing an N-terminal deleted PDE protein by the method of Lee et al. because the PDE proteins of Lee et al. and Bolger et al. are structurally very closely related such that a skilled artisan would expect them to have similar crystallization properties.

Conclusion

Status of the claims:

Claims 1-14 and 43 are pending.

Claims 1-14 and 43 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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